Zika and Spondweni viruses: Historic evidence of misidentification, misdiagnosis, and serious clinical disease manifestations

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Abstract

The Spondweni serogroup (family *Flaviviridae*, genus *Flavivirus*) consists of two members: Zika and Spondweni viruses. Both viruses have been historically misidentified and their diseases have been misdiagnosed due to their serological cross-reactivity and similar clinical presentations. Within historic case reports a sub-set of patients has presented with short duration clinical manifestations suggestive of more serious illness.

Perspective

Viruses within the genus *Flavivirus*, family *Flaviviridae*, are notorious for their serological cross-reactivity. Prior to the advent of genetic sequencing, classic serological assays such as the virus neutralization and hemaggutination-inhibition were used to differentiate the various species of arboviruses. Although not perfect, much of the early work differentiating flaviviruses into various serogroups was later confirmed by sequencing and phylogenetic analyses. Historically, serological assays (the neutralization and complement fixation tests) were also used to determine the prevalence of prior infection and geographic distribution of flaviviruses. Both viruses in the Spondweni serogroup, Zika (ZIKV) and Spondweni (SPONV), exhibit serological cross-reactivity and non-specific febrile illness, making diagnosis challenging in regions where both viruses co-circulate.

ZIKV was first isolated in Uganda in 1947 (strain MR-766) (1) and SPONV was first isolated in Nigeria in 1952 (strain Chuku) (2). Cross-reactivity using the neutralization test led to the misidentification of the SPONV Chuku strain isolated by MacNamara in 1952 as a strain of ZIKV (2-5). This misidentification led to additional studies where this strain of SPONV was reported as ZIKV – confusion that continues to the present day, although the misidentification of this isolate was clarified and widely reported in 1964 (3-5). Consequently, the clinical case reports by MacNamara (2), the work by Bearcroft (6) involving the experimental infection of a human volunteer and vector competence studies in *Aedes aegypti* mosquitoes, and the experimental work by Bearcroft (7) in *Macaca mulatta* monkeys investigating the effect of prior infection, and the subsequent histopathology of the liver and level of cross-protection following exposure to yellow fever virus, all utilized SPONV (Chuku strain) rather than ZIKV. Furthermore, early serosurveys in regions where both ZIKV and SPONV co-circulate are suspect due to serological cross-reactivity or where serological assays only screened for one of the two viruses (2, 8).

Both ZIKV and SPONV are arthropod-borne viruses and utilize a mosquito/host (non-human primate and/or human) transmission cycle. ZIKV has a wide geographic distribution that includes East and West Africa, the Indian sub-continent, Southeast Asia, Oceania, South and Central America, and the Caribbean (9-11); whereas SPONV has thus far only been reported from sub-Saharan Africa (12). The lack of continuous historic detection in those regions with ZIKV or SPONV isolations or serological evidence of transmission prior to 2007 is likely due to the lack of surveillance, misdiagnosis, and under-reporting. It is plausible that virus outbreaks did occur in those regions with prior serologic evidence of infection and were attributed to other arboviral infections. Clinical ZIKV and SPONV presentation is similar to classic dengue fever which may have led to historic misdiagnosis (9).

In their historic geographic ranges (distribution prior to 2007), both ZIKV and SPONV likely circulated at low levels in sylvatic cycles, whereby low numbers of naïve persons were periodically exposed to infection. While historic case reports of serious clinical manifestations associated with Spondweni Serogroup viruses may have been limited due to poor diagnosis and reporting, it is plausible that the lack of historic reports of congenital birth defects associated with ZIKV infection *in utero*, were a result of exposure to the virus prior to puberty. Such an infection would likely result in a female being immune to a subsequent infection during her reproductive years. The extent of cross-protection exhibited within the Spondweni Serogroup is unknown, and cross-protection with other flaviviruses such as yellow fever virus and/or the 17D yellow fever virus vaccine appears to be limited (4-6, 13-16).

Most cases of ZIKV and SPONV infection are asymptomatic (10, 11). Of symptomatic cases, signs and symptoms appear as early as 3 days following infection for both ZIKV(11) and SPONV (6). The common clinical presentation of ZIKV infection is now well established and a recent literature review lists the most common signs and symptoms reported from 195 patients from 1964 to 2016 as rash (67.2%), fever (63.6%), arthralgia (28.7%), myalgia (23.6%), headache (21.5%), conjunctivitis (20.5%), retro-orbital pain (11.3%), edema (9.7%), puritus (7.7%) and fatigue (7.2%) (11). Less is known regarding the clinical presentation of SPONV as there are few well documented clinical cases reported in the literature (n = 6). The most common signs and symptoms reported in those SPONV cases include: fever (100%), headache (83.3%), nausea (83.3%), myalgia (66.6%), arthralgia (50.0%), vertigo (33.3%), conjunctivitis (16.7%), macropapular and pruritic rash (16.7%), and epistaxis (16.7%), photophobia (16.7%), vomiting (16.7%), and disorientation (16.7%) (2, 5, 6, 13, 16). It is clear that both ZIKV and SPONV display similar signs and symptoms making diagnosis difficult in regions where both viruses co-circulate, additionally there are no commercially available serological assays that can differentiate these two viruses. In regions where both viruses co-circulate, diagnosis requires a monotypic reaction to a given serologic assay, PCR confirmation, or virus isolation.

While most symptomatic ZIKV and SPONV infections present as a mild to moderate febrile illness, a sub-set of cases present with short duration clinical manifestations suggestive of more serious illness. Prior to reports of ZIKV in the Western Hemisphere, Spondweni Serogroup case reports included: conjunctivitis (ZIKV and SPONV), macropapular rash (ZIKV and SPONV), pruritic rash (SPONV), hematuria (ZIKV), hematospermia (ZIKV), apthous ulcer (ZIKV), and epistaxis (SPONV) indicating vascular leakage; and reports of photophobia (ZIKV and SPONV), vomiting (ZIKV and SPONV), vertigo (SPONV), disorientation (SPONV), meningismus (SPONV), and bilateral transient ocular paresis (SPONV) were indicative of neurological involvement (2, 5, 6, 13, 16, 17). Additionally, Guillain-Barré syndrome (18), evidence of sexual transmission (15), and evidence perinatal transmission (19) were all associated with a sub-set of ZIKV cases prior to the introduction of the virus in the Western Hemisphere.

In summary, symptomatic cases of ZIKV and SPONV infection present with similar signs and symptoms and anti-ZIKV and anti-SPONV serological assays exhibit cross-reactivity. Early work by MacNamara (1954) and Bearcroft (1956 and 1957) misidentified SPONV as ZIKV. Prior to the introduction of ZIKV into the Western Hemisphere there was evidence of clinical manifestations indicative of vascular leakage and neurological involvement within the Serogroup as well as unique transmission mechanisms associated with a sub-set of patients infected with ZIKV.

Authors' contributions

ADH and JPW both contributed equally to researching historic reports and writing the manuscript.

Disclosure Statement

The views expressed in this article are those of the authors and do not reflect the official policy or position of the U.S. Department of Defense or the Department of the Army.

Competing interests

The authors have no financial, personal, or professional interests that inappropriately influenced this paper.

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